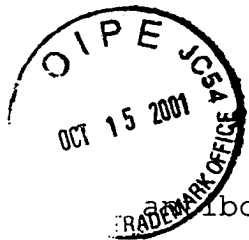


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APPENDIX A

56. (Twice amended) An enhanced LM609 grafted antibody exhibiting selective binding affinity to  $\alpha_v\beta_3$ , or a functional fragment thereof, comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8, said antibody or functional fragment thereof having integrin  $\alpha_v\beta_3$  binding activity, integrin  $\alpha_v\beta_3$  binding specificity or integrin  $\alpha_v\beta_3$ -inhibitory activity, wherein the  $\alpha_v\beta_3$  binding affinity of said enhanced LM609 grafted antibody is maintained relative to parental LM609 grafted antibody.

60. (Amended) The enhanced LM609 grafted antibody of claim [59] 107, wherein said  $V_H$  CDR1 is selected from the group consisting of the CDRs referenced as SEQ ID NO:48, SEQ ID NO:50 and SEQ ID NO:52.

61. (Amended) The enhanced LM609 grafted antibody of claim [59] 107, wherein said  $V_H$  CDR2 is selected from the group consisting of the CDRs referenced as SEQ ID NO:54, SEQ ID NO:56 and SEQ ID NO:58.

62. (Amended) The enhanced LM609 grafted antibody of claim [59] 107, wherein said  $V_H$  CDR3 is selected from the group consisting of the CDRs referenced as SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID

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NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80,  
SEQ ID NO:94, SEQ ID NO:96; SEQ ID NO:98 and SEQ ID NO:100.

63. (Amended) The enhanced LM609 grafted antibody of claim [59] 107, wherein said V<sub>L</sub> CDR1 is the CDR referenced as SEQ ID NO:82.

64. (Amended) The enhanced LM609 grafted antibody of claim [59] 107, wherein said V<sub>L</sub> CDR2 is the CDR referenced as SEQ ID NO:84.

65. (Amended) The enhanced LM609 grafted antibody of claim [59] 107, wherein said V<sub>L</sub> CDR3 is selected from the group consisting of the CDRs referenced as SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90 and SEQ ID NO:92.

67. (Amended) The enhanced LM609 grafted antibody of [claims] claim 66, wherein said functional fragment is selected from the group consisting of Fv, Fab, F(ab)<sub>2</sub> and scFV.

69. (Amended) The enhanced LM609 grafted antibody of claim [68] 107, wherein said enhanced LM609 grafted antibody comprises the combination of CDRs selected from the group consisting of:

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

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the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:72;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:70;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:72;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:86, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90 and V<sub>H</sub> CDR3 referenced as SEQ ID NO:68; and

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and V<sub>H</sub> CDR3 referenced as SEQ ID NO:68.

71. (Amended) The enhanced LM609 grafted antibody of [claims] claim 70, wherein said functional fragment is selected from the group consisting of Fv, Fab, F(ab)<sub>2</sub> and scFV.

73. (Amended) The enhanced LM609 grafted antibody of claim [72] 107, wherein said enhanced LM609 grafted antibody comprises the combination of CDRs selected from the group consisting of:

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:94;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90, the V<sub>H</sub> CDR2

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referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:94;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:96;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:94;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:98; and

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:100.

74. (Twice amended) A high affinity LM609 grafted antibody exhibiting selective binding affinity to  $\alpha_v\beta_3$ , or a functional fragment thereof, comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8, said antibody or functional fragment thereof having integrin  $\alpha_v\beta_3$  binding activity, integrin  $\alpha_v\beta_3$  binding specificity or integrin  $\alpha_v\beta_3$ -inhibitory activity, wherein the  $\alpha_v\beta_3$  binding affinity of said high affinity LM609 grafted antibody is [enhanced] higher affinity relative to parental LM609 grafted antibody.

77. (Amended) The high affinity LM609 grafted antibody of claim [76] 108, wherein said high affinity LM609 grafted antibody comprises the combination of CDRs selected from

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the group consisting of:

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:72;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:70;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:72;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:86, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:94;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90 and V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:94;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90, the V<sub>H</sub> CDR2

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referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:96;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:94;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:98; and

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:100.

80. (Amended) [An] The antibody of claim 109, or functional fragment thereof, comprising a V<sub>H</sub> CDR1 selected from the group consisting of the CDRs referenced as SEQ ID NO:48, SEQ ID NO:50 and SEQ ID NO:52.

82. (Amended) [An] The antibody of claim 109, or functional fragment thereof, comprising a V<sub>H</sub> CDR2 selected from the group consisting of the CDRs referenced as SEQ ID NO:54, SEQ ID NO:56 and SEQ ID NO:58.

84. (Amended) [An] The antibody of claim 109, or functional fragment thereof, comprising a V<sub>H</sub> CDR3 selected from the group consisting of the CDRs referenced as SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:94, SEQ ID NO:96; SEQ ID NO:98 and SEQ ID NO:100.

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86. (Amended) [An] The antibody of claim 109, or functional fragment thereof, comprising a V<sub>L</sub> CDR1 referenced as SEQ ID NO:82.

88. (Amended) [An] The antibody of claim 109, or functional fragment thereof, comprising a V<sub>L</sub> CDR2 referenced as SEQ ID NO:84.

90. (Amended) [An] The antibody of claim 109, or functional fragment thereof, comprising a V<sub>L</sub> CDR3 selected from the group consisting of the CDRs referenced as SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90 and SEQ ID NO:92.

92. (Amended) [An] The antibody of claim 109, or functional fragment thereof, comprising the combination of CDRs selected from the group consisting of:

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:72;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:70;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82 and the V<sub>H</sub> CDR3

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referenced as SEQ ID NO:72;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:86, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90 and V<sub>H</sub> CDR3 referenced as SEQ ID NO:68; and

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and V<sub>H</sub> CDR3 referenced as SEQ ID NO:68.

93. (Amended) The antibody of [claims] claim 92, wherein said functional fragment is selected from the group consisting of Fv, Fab, F(ab)<sub>2</sub> and scFV.

94. (Amended) [An] The antibody of claim 109, or functional fragment thereof, comprising the combination of CDRs selected from the group consisting of:

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:94;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:94;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:96;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:94;



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the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:98; and

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:90, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:100.

95. (Amended) The antibody of [claims] claim 94, wherein said functional fragment is selected from the group consisting of Fv, Fab, F(ab)<sub>2</sub> and scFV.

96. (Amended) [An] The antibody of claim 109, or functional fragment thereof, comprising the combination of CDRs selected from the group consisting of:

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:68;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:72;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:70;

the V<sub>L</sub> CDR1 referenced as SEQ ID NO:82 and the V<sub>H</sub> CDR3 referenced as SEQ ID NO:72;

the V<sub>L</sub> CDR3 referenced as SEQ ID NO:86, the V<sub>H</sub> CDR2 referenced as SEQ ID NO:56 and the V<sub>H</sub> CDR3 referenced as SEQ ID

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NO:68;

the  $V_L$  CDR3 referenced as SEQ ID NO:90, the  $V_H$  CDR2 referenced as SEQ ID NO:56 and the  $V_H$  CDR3 referenced as SEQ ID NO:94;

the  $V_L$  CDR3 referenced as SEQ ID NO:90 and  $V_H$  CDR3 referenced as SEQ ID NO:68;

the  $V_L$  CDR3 referenced as SEQ ID NO:90, the  $V_H$  CDR2 referenced as SEQ ID NO:56 and  $V_H$  CDR3 referenced as SEQ ID NO:68;

the  $V_L$  CDR1 referenced as SEQ ID NO:82, the  $V_H$  CDR2 referenced as SEQ ID NO:56 and the  $V_H$  CDR3 referenced as SEQ ID NO:94;

the  $V_L$  CDR3 referenced as SEQ ID NO:90, the  $V_H$  CDR2 referenced as SEQ ID NO:56 and the  $V_H$  CDR3 referenced as SEQ ID NO:96;

the  $V_L$  CDR3 referenced as SEQ ID NO:90 and the  $V_H$  CDR3 referenced as SEQ ID NO:94;

the  $V_L$  CDR3 referenced as SEQ ID NO:90 and the  $V_H$  CDR3 referenced as SEQ ID NO:98; and

the  $V_L$  CDR3 referenced as SEQ ID NO:90, the  $V_H$  CDR2 referenced as SEQ ID NO:56 and the  $V_H$  CDR3 referenced as SEQ ID NO:100.